European Journal of Ophthalmology / Vol. 17 no. 2, 2007 / pp. 151-159

A comparison of the effect of carbomer-, cellulose-, and mineral oil-based artificial tear formulations

I.-J. WANG, I.-C. LIN, Y.-C. HOU, F.-R. HU

Department of Ophthalmology, National Taiwan University Hospital, Taipei - Taiwan

PURPOSE. *To compare the efficacy, safety, and local tolerance between carbomer-based artificial tears, cellulose-, and mineral oil-based artificial tears.*
METHODS. *A randomized, open-label, parallel-group comparative 28-day study was designed for 67 patients who were randomized into three treatment groups. Measurements included the scoring of total subjective symptoms and objective signs, Schirmer-Jones test values, and tear break-up time (BUT) at baseline, and after 2 and 4 weeks of treatment. Safety of study treatment was also assessed. Outcomes measured at baseline and 2 and 4 weeks follow-up included the scoring of total subjective symptoms and objective signs, Schirmer-Jones test values, and tear BUT, subjective assessments, and safety.*
RESULTS. *There were no differences regarding total scores, Schirmer-Jones test, or tear BUT at baseline among these three groups at 2 and 4 weeks. Patients in all three treatment groups experienced a significant improvement from baseline in total scores and Schirmer-Jones test values after treatment. Subjective assessment was better with carbomer-based treatment.*
CONCLUSIONS. *Each artificial tear formulation successfully relieved symptoms and signs of keratoconjunctivitis sicca. The tolerance of carbomer-based artificial tears was comparable to that of cellulose- and mineral oil-based artificial tears. (Eur J Ophthalmol 2007; 17: 151-9)*

KEY WORDS. *Carbomer-based artificial tears, Cellulose-based artificial tears, Mineral oil-based artificial tears, Keratoconjunctivitis sicca*

Accepted: September 1, 2006

INTRODUCTION

Keratoconjunctivitis sicca (KCS) is an eye disorder characterized by a deficiency in or increased evaporation of the tear film (1). Subjective symptoms accompanying KCS include a gritty or foreign body sensation, burning sensation, dry eye sensation, photophobia, and others (2). Objective signs include conjunctival hyperemia, foamy tears, conjunctival mucous threads, corneal epithelial filaments, and fluorescein staining of the cornea (2).

Although most patients with dry eye benefit from a marked symptomatic improvement with artificial tears, the efficacy of many tear substitutes may be affected by their formulations and retention times (3-5). For example, while an oil-based formulation appears to have a longer retention time, it is usually associated with feelings of stickiness and markedly prolonged durations of blurred vision. Cellulose-based artificial tears have a shorter retention time, which requires frequent application (6). Carbomer-based artificial tear formulations such as that of polyacrylic

 1120-6721/151-09$15.00/0

acid 0.2%, also called carbopol 940 or carbomer, have been reported to maintain the tear film in contact with the eye for a shorter time compared with mineral oil-based artificial tear preparations, but for longer than cellulose-based artificial tear preparations (5). Appropriate use and selection of artificial tears is important in each different individual because compliance and subjective feelings are different. We therefore designed our 28-day treatment study to compare the efficacy, safety, and local tolerance between carbomer-based, cellulose-based, and mineral oil-based artificial tears in patients with dry eyes.

MATERIALS AND METHODS

A randomized, open-label, parallel-group comparative study was conducted at National Taiwan University Hospital between February 2003 and January 2005. This study complied with the Declaration of Helsinki. All patients gave informed consent after receiving an explanation of the nature and possible consequences of the study; its protocol was reviewed and approved by the institutional review board. Eighty patients with dry eye fulfilled the diagnostic criteria of deteriorated tear function and ocular surface abnormalities proposed by the NEI/Industry workshop on dry eye (7). All patients had to have at least one of the following signs of dry eyes in both eyes: Schirmer-Jones test (with anesthesia) values of 5 mm of wetting or less in 5 minutes in both eyes (8); a tear break-up time (BUT) of ≤10 seconds. Triple classification of dry eye was applied to these patients (9). Only dry eyes with grade II severity (i.e., symptoms with reversible signs) have been included in the study, and ones with grade III (symptoms with permanent signs) have been excluded.

Basic tearing was assessed by the Schirmer-Jones test in which the cornea was anesthetized (two drops of oxybuprocaine 0.4%) and the lid margin was dried thoroughly. Three minutes later, a pre-calibrated sterile strip (Schirmer Plus® Laboratory, Pharma+, Orleans, France) was placed in the lower temporal fornix in the junction of the middle and outer third of the lower lid. After 5 minutes with the eyelids closed, the length of wetting was recorded: all dry eye patients had Schirmer-Jones values of <5 mm. The ocular surface was examined by placing a 2 µL volume of a preservative-free fluorescein dye (1.0%) in the conjunctival sac, and the BUT was measured three times to obtain an individual's average measurement. Symptoms of dry eye were recorded and included dryness, burning, foreign body sensation, photophobia, pain, or difficulty in opening eyes after sleeping. The main exclusion criteria were age <18 years, systemic therapy such as beta-blockers that could influence lacrimal secretion, naso-lacrimal obstruction, external eye disease inducing conjunctiva inflammation and/or infection and corneal scars, contact lens usage, any local treatment with eye drops and/or ointment other than for dry eye, and noncompliance with protocol (e.g., attendance and completion of patient diary). If the patients used eye drops and/or ointment for dry eye before the study, they must have had a 1-month washout period before this study. Patients with Sjögren syndrome treated with oral steroids were excluded.

Patients were randomized to one of three treatment groups. Group 1 patients were treated with carbomer-based artificial tears (carbomer MW 4,000,000 0.2%, sorbitol 4%, NaOH 0.084%, cetrimide 0.01%, EDTA 0.01%, pH 7.3, viscosity 4.5 mP, osmolarity 250 mOsm/kg, refractive index 1.338; Vidisic Ophthalmic Gel, Dr. Gerhard Mann, Germany) four times daily. Group 2 patients were treated with cellulose-based artificial tears (dexpanthenol 3%, hypromellose 0.32%, sorbitol 1.5%, Na2HPO4 0.462%, NaH2PO4 0.1%, cetrimide 0.01%, pH 7.3, viscosity 10 mP, osmolarity 300 mOsm/kg, density 1.3405, refractive index 1.3405; Artelac Ophthalmic Solution, Dr. Gerhard Mann) four times a day. Group 3 patients were treated with mineral oil-based artificial tears (3% of anhydrous liquid lanolin [Lantrol] in a mineral oil base with methylparaben 0.05% [m/m] and propylparaben 0.01% [m/m] as preservatives; Duratears Ointment, Alcon) one time before sleep.

Subjective symptoms included foreign body sensation, burning sensation, dry eye sensation, itching, and pain. They were assessed on a four-point scale measuring scores from 0 to 3 as follows: 0=absent; 1=mild (present but not distressing); 2=moderate (distressing but not interfering with daily life); 3=severe (very distressing and interfering with daily life). Objective signs included bulbar conjunctival injection and fluorescein staining of the cornea. The degree of fluorescein staining (0.5%) was assessed as follows: 0 = no fluorescein stain, or <5 superficial punctate erosions, 1 = >5 erosions affecting less than 10% of the cornea; 2 = erosions affecting 10 to 25% of the sur-

face; 3 = erosions affecting >50% of the surface; 4 = presence of confluent erosions affecting one or more zones; microulcerations; 5 = presence of one or more side and deep corneal ulcers. Both injections of palpebral and bulbar conjunctiva were evaluated at each visit. These signs were graded on a four-point scale measuring scores from 0 to 3 as follows: 0 = vessels normal; 1 = some vessels definitely injected; 2 = diffusely injected eye but with individual vessels still discernible; and 3 = intensely red eye with individual vessels not easily seen.

The objective examinations included Schirmer-Jones test values, tears BUT, and patient subjective assessment of study treatment. The measurements were conducted at day 0 (baseline) and at weeks 2 and 4. The symptoms and signs were recorded for both eyes.

Local tolerance was evaluated at weeks 2 and 4 by grading the following complaints that occurred immediately after instillation of the study medication: burning sensation, blurred vision, pain, sticky eyelids. The grading was on a four-point scale with a scale of 0 to 3, similar to that used to assess the symptoms of dry eyes.

No study medication was used for at least 2 hours prior to the ophthalmic examination on days 14 and 28 of the study, to enable a more accurate assessment of the improvement in the dry eye condition.

Statistical analysis

The demographic characteristics were compared among the three groups at baseline with Fisher exact test for categorical variables and *t*-test for continuous variables. The analysis of variance (ANOVA) was used to account for any potential covariate such as baseline and demographic variables when investigating the difference in efficacy endpoints between two groups. Changes in symptoms and signs were assessed by chi-square tests of independence in two-way and multiple-way tables. Continuous variables, total signs and symptoms recorded, tear BUT, and Schirmer-Jones test were analyzed by ANOVA using Bonferroni criteria. Data analyses and summaries of the efficacy and safety endpoints were performed in the following populations: intention to treat (ITT) population – all randomized patients who had received the study medication and who had at least one follow-up evaluation, regardless of their compliance with the protocol or their eligibility to the study; safety population – patients who had received at least one dose of the study medication. The ITT population was used to analyze the efficacy endpoints and the safety population was used in the analysis of the safety endpoints. If a patient missed the last follow-up visit, the last observation carried forward (LOCF) method was adopted to replace the missing value (10).

RESULTS

Characteristics of the patients

A total of 80 patients were screened and randomized into one of three treatment groups (28 to the carbomer-based group, 26 to the cellulose-based group, and 26 to the mineral oil-based group). Thirteen patients were excluded as protocol deviations, leaving 67 patients for analysis in the ITT and safety populations. All protocol deviations consisted of ineligibility, off-window visits, et cetera.

Demographic and other baseline characteristics

Sixty-seven patients were included in the ITT analysis. In the ITT population, the mean age was 55.86 years in the carbomer-based group, 50.08 years in the cellulose-based group, and 60.31 years in the mineral oil-based group; distribution among the three groups was comparable (p=0.053). There were more females than males in each group. The sex distribution between three groups was comparable (p=0.561) (Tab. I).

Efficacy

Symptom scores and signs were measured at baseline and on days 14 and 28. Figure 1 shows that, at baseline, the mean total scores were 12.95 in the carbomer-based group, 16.61 in the cellulose-based group, and 13.59 in the mineral oil-based group. Although patients in the cellulose-based group appeared to have a higher baseline score than the other two groups, the difference did not achieve statistical significance (p>0.05), which indicates that the three groups were

TABLE I - BASELINE DEMOGRAPHICS OF TREATMENT GROUPS

	Carbomer-based	Cellulose-based	Mineral oil-based	p value (ANOVA)
No.	22	23	22	
Age, yr, mean ± SD	55.86 ±15.66	50.08±14.32	60.31±11.21	0.053
Sex				0.561
F	19	17	19	
M	3	6	3	
Reasons for dry eyes (Fisher exact test)				0.293
	17	17	20	
Keratoconjunctivitis sicca				
Secondary	3	5	1	
Primary	2	1	0	
Other	0	0	1	

ANOVA = Analysis of variance

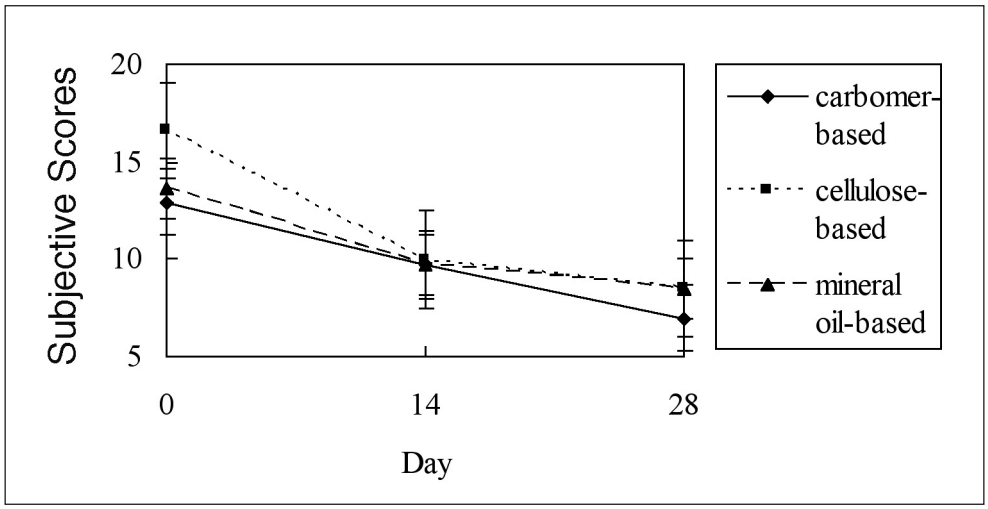

Fig. 1 - *Comparison of total subjective symptoms and objective sign scores among patients in carbomer, cellulose-, and mineral oil-based groups.*

comparable. After 2 weeks of treatment, significant improvements were observed in all three groups. The mean total score was reduced by 6.65 in the carbomer-based group, by 3.48 in the cellulose-based group, and by 3.95 in the mineral oil-based group. At the end of study, the mean total score was reduced by 8.09 in the carbomer-based group, by 6.47 in the cellulose-based group, and by 3.83 in the mineral oil-based group; there were no significant between-group differences (Fig. 1).

Figure 2 shows that there were no significant between-group differences at baseline regarding Schirmer-Jones test mean values (3.86, 3.73, and 2.77 for the carbomer-based group, the cellulose-based group, and the mineral oil-based group, respectively; p=0.434). After 2 weeks' treatment, Schirmer-Jones test mean values for the right eye were significantly improved from baseline in all three groups (5.30, 3.69, and 3.18 for the carbomer-based group, the cellulose-based group, and the mineral oil-based group, respectively; ANOVA with repeated measurement, p>0.05); after 4 weeks' treatment, corresponding mean values had increased to 5.89, 6.91, and 3.61, respectively (ANOVA with repeated measurement, p=0.001). A post hoc Tukey evaluation showed that Schirmer-Jones values were increased from baseline by a significantly greater extent with carbomer- and cellulose-based formulations than with the mineral-oil based formulation

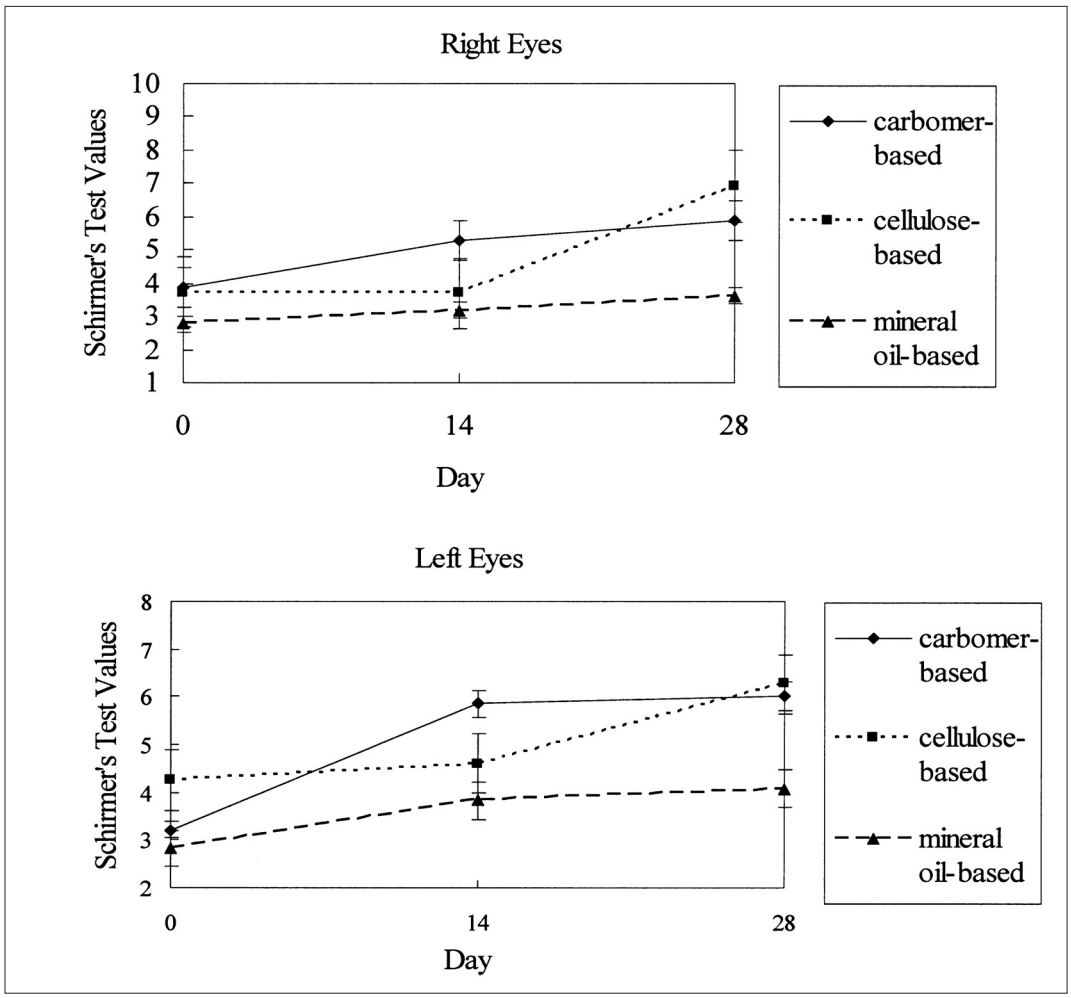

Fig. 2 - *Comparison of changes in Schirmer-Jones test values among patients in carbomer-, cellulose-, and mineral oil-based groups.*

($p<0.05$). The same trends were observed in the left eyes.

Figure 3 shows that, in the right eye, there were no significant between-group differences in tear BUT at baseline ($p=0.679$). After 2 weeks' treatment, tear BUT was significantly improved from baseline in all three groups; there was no statistical between-group significance (ANOVA with repeated measurement, $p>0.05$). After 4 weeks' treatment, mean values were further increased to 8.32 in the carbomer-based group, 6.20 in the cellulose-based group, and 6.89 in the mineral oil-based group (ANOVA with repeated measurement, $p<0.001$). A post hoc Tukey evaluation showed that Schirmer-Jones values were increased from baseline by a significantly greater extent with carbomer-based formulations, compared with cellulose- and mineral oil-based formulations ($p<0.05$). The tear BUTs of left eyes show the same trend as that seen for the right eyes.

Patients assessed the overall efficacy of the study drugs by using a four-point rating scale (excellent, good, fair, and poor) (Tab. II). The assessment was done during treatment at week 2 and after treatment at week 4. At the initial assessment during treatment (week 2), a greater number of patients reported a good response with the carbomer-based formulation, compared with the cellulose- or mineral oil-based formulations (8 vs 5 and 2, respectively). The majority of patients were assessed to have a fair response during the treatment period (carbomer-based group 10; cellulose-based group 15; mineral oil-based group 14%). The same pattern of response was also seen upon assessment after treatment. An excellent response was reported by only one patient, who received carbomer-based treatment. A good response was reported by more patients in the carbomer-based group (11) compared with recipients of cellulose-based treatment (5)

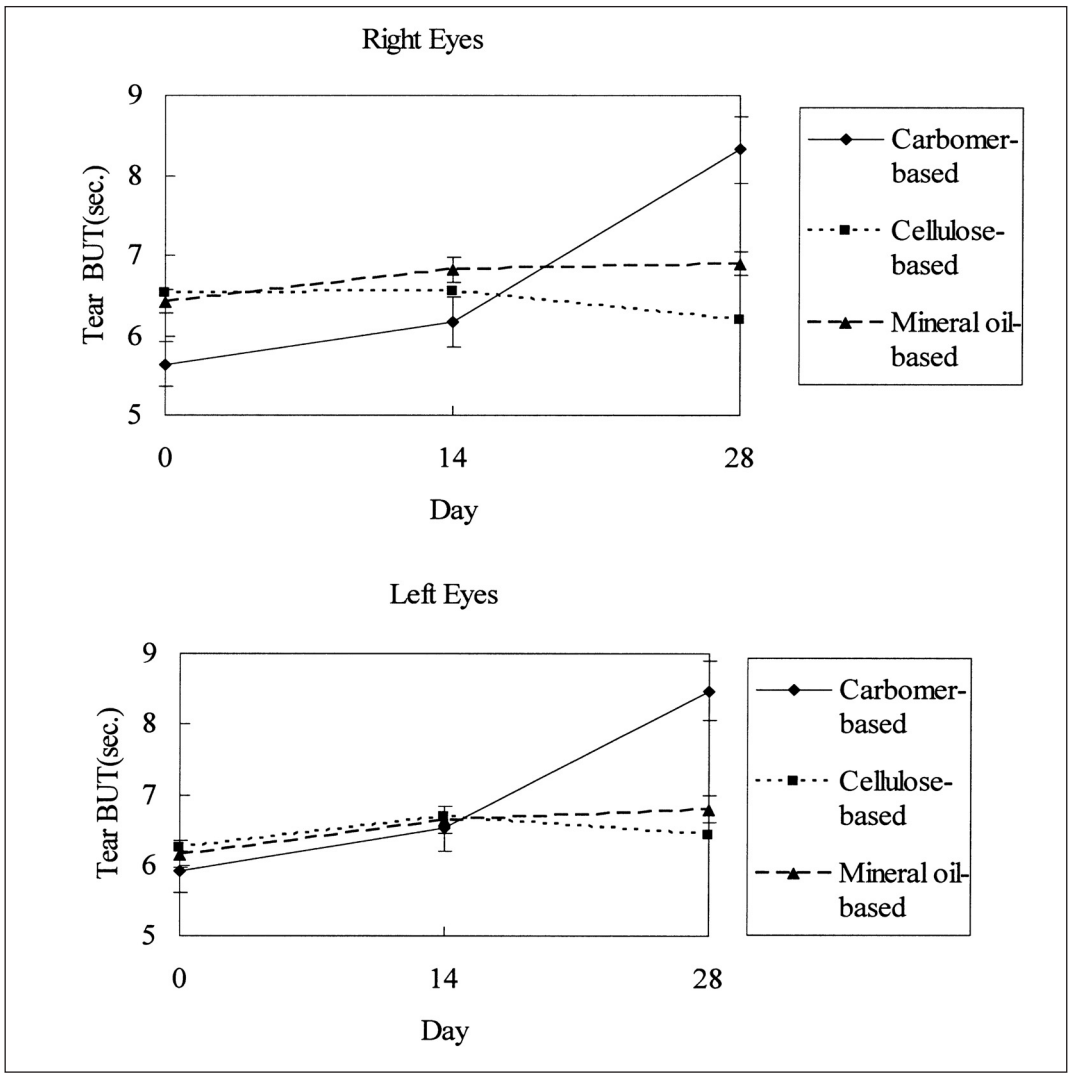

Fig. 3 - *Comparison of tear film break-up time among patients in carbomer-, cellulose-, and mineral oil-based groups.*

or mineral oil-based treatment (3). Most of the patients treated with cellulose-based and mineral oil-based formulations reported a fair response to treatment (15 and 12, respectively).

Safety

The population for safety evaluation was defined as all randomized patients who received at least one study medication. Safety of the three study drugs was assessed by local tolerance at weeks 2 and 4. Table III shows that, between weeks 2 and 4, in the carbomer-based group, there was a decreased trend in the symptoms of burning sensation and blurred vision, and an increased trend in sticky eyelids; in the cellulose-based group and the mineral oil-based group, decreases were observed in all symptoms (burning sensation, blurred vision, and sticky eyelids). No significant between-group differences were observed.

DISCUSSION

Current therapy for the treatment of ocular irritation associated with dry eye is aimed at symptomatic relief (11). Treatment options include the use of artificial tears, ocular lubricants, punctal occlusion, moisture goggles, and tarsorrhaphy. Topically applied ocular lubricants, or artificial tears, are the mainstay of treatment. The supplementation of existing tears with artificial tears, although a commonly prescribed treatment, often only provides temporary relief for

TABLE II - CHANGES IN PATIENT SUBJECTIVE ASSESSMENTS

	Carbomer-based n	Cellulose-based n	Mineral oil-based n	p value (Fisher exact test)
Day 14				0.254
Excellent	0	0	0	
Good	8	5	2	
Fair	10	15	14	
Poor	3	3	5	
Day 28				<0.00001
Excellent	1	0	0	
Good	11	5	3	
Fair	6	15	12	
Poor	4	3	7	

TABLE III - SAFETY EVALUATION (LEFT EYE)

	Carbomer-based n=21	Cellulose-based n=23	Mineral oil-based n=21	p value (ANOVA)
Day 14				
Burning sensation	0.29±0.56	0.26±0.62	0.24±0.56	0.965
Blurred vision	0.62±0.67	0.7±0.82	0.95±0.8	0.344
Sticky eyelids	0.33±0.48	0.43±0.51	0.67±0.73	0.171
Day 28				
Burning sensation	0.26±0.56	0.09±0.29	0.17±0.38	0.434
Blurred vision	0.53±0.77	0.64±0.79	0.72±0.75	0.742
Sticky (strand) eyelids	0.58±0.61	0.32±0.48	0.5±0.51	0.280

Values are mean ± SD.
ANOVA = analysis of variance

the patient after single or multiple instillations and does not reverse the cellular pathology (12). Moreover, frequent instillation of artificial tears is a major disadvantage of such treatment for dry eye syndrome. Other formulations, including gel-based, cellulose-based, and mineral oil-based preparations, have been shown to relieve symptoms of dry eye and have been proposed as alternatives to classic liquid formulations, because of their prolonged retention times, compared with aqueous tear substitutes (13, 14).

In the current study, we have shown that each of the carbomer-based, cellulose-based, and mineral oil-based formulations can relieve subjective symptoms after 2 weeks and 4 weeks of treatment. Our results differed from those of Marner et al and Brodwall et al, which revealed that carbomer ocular gel was used significantly less frequently when compared with polyvinylalcohol eye drops and resulted in a significantly better reduction of total symptoms score and prolongation of tear BUT, although the gel-based preparation was associated with significantly more adverse events (15, 16). We were unable to find any published evidence comparing the efficacy, tolerance, and symptoms scores among the three formulations as mentioned above. In regard to subjective symptoms, our study shows that these three formulations are clinically compatible and useful for dry eye patients. They can relieve symptoms of foreign body sensation, burning sensation, dry eye sensation, itching, and pain. Blurred vision is the most common adverse event cited with the use of these artificial tears (15, 16). This symptom is probably due to the higher viscosity and increased ocular retention times that are associated

with polyacrylic acid. In the majority of cases, blurred vision was reported as being transient. In addition, Leibowitz et al reported a single non-mask study using carboxymethlyene gel in 55 patients with severe dry eyes (5). The report noted that administering too much gel caused stinging and blurring. When properly instilled, the gel tended to adhere to the surface of the conjunctiva deep in the lower fornix and remained in this location. Only occasionally did a bolus of formed gel migrate from the lower fornix to the axial cornea and cause blurred vision. Vigorous blinking and manipulation of the lower lid eliminated the problem.

Interestingly, both carbomer-based and cellulose-based artificial tears increased Schirmer-Jones test and tear BUT values after 4 weeks of treatment. We surmise that these outcomes are due to the treatments inducing prolonged retention times of tears in the ocular surface and an increased stability of tear film. Toda et al demonstrated that unpreserved hydroxypropyl methylcellulose could improve tear BUT values in patients with Sjögren syndrome (17). In addition, Brodwall et al have shown that carbomer-based and polyvinylalcohol formulations are associated with improvements in Schirmer-Jones and tear BUT values in dry eyes (16). Therefore, our results are compatible with those of previous studies.

Furthermore, although the higher viscosity of these gels and oil-based formulations presumably prolongs tear retention time in the eye and therefore requires fewer daily applications, toxicology studies with gel formulations have shown that carbomer gel preparations are more toxic than carboxymethylcellulose artificial tears formulations (18).

In our study, an excellent response was reported by only one patient. This patient received carbomer-based treatment. More patients reported a good response in the carbomer-based group (42%) than in the cellulose-based group (23%) or mineral oil-based group (16%). The majority of patients who received cellulose-based or mineral oil-based treatment recorded a fair response to treatment, 64% and 44%, respectively. Thus, a carbomer-based formulation may be expected to prolong symptomatic relief and reduce application frequency in patients with dry eyes. Another advantage is that, with every eyelid movement, a clear aqueous gel is converted into a fluid. This ensures clear vision without any feelings of stickiness. At the same time, a stable, long-lasting tear film may be formed, so ensuring that four times daily application is an effective therapy, even in severe cases of keratoconjunctivitis sicca (19).

Our study provides supportive evidence that these three drugs successfully relieve the symptoms of dry eye and suggests that they are appropriate in the management of this disorder. Sullivan et al have reported a single-masked, placebo-controlled study using carbomer gel in 123 patients with moderate to severe dry eyes (13). The results demonstrate that carbomer gel was more efficacious than placebo in improving subjective and objective symptoms. Our study provides further evidence that topical treatment with carbomer-based artificial tears is as effective as cellulose-based and oil-based artificial tears in reducing the number of total subjective symptoms and scores for objective signs, and in increasing Schirmer-Jones and tears BUT values after 2 and 4 weeks of treatment. However, the compositions of these three drugs are different; there may be some limitations to the present study. If the composition is the same, the comparison between these tears formulas is more valuable. Therefore, it is necessary to conduct studies comparing artificial tears with the same composition but different formulas in a further project.

Proprietary interest: None.

Reprint requests to:
Dr. I.-Jong Wang
Department of Ophthalmology
National Taiwan University Hospital
7 Chung-Shan South Road
Taipei, Taiwan
ijong@ha.mc.ntu.edu.tw

REFERENCES

1. Lemp MA. Epidemiology and classification of dry eye. Adv Exp Med Biol 1998; 438: 791-803.
2. Dohlman CH, Lemp MA, English FP. Dry eye syndromes. Int Ophthalmol Clin 1970; 10: 215-51.
3. Bach FC, Adam JB, McWhirter HC, Johnson JE. Ocular retention of artificial tear solutions. Comparison of hydroxypropyl methylcellulose and polyvinyl alcohol vehicles using an argyrol marker. Ann Ophthalmol 1972; 4: 116-9.
4. Holly FJ. Artificial tear formulations. Int Ophthalmol Clin 1980; 20: 171-84.
5. Leibowitz HM, Chang RK, Mandell AI. Gel tears. A new medication for the treatment of dry eyes. Ophthalmology 1984; 91: 1199-204.
6. Swanson M. Compliance with and typical usage of artificial tears in dry eye conditions. J Am Optom Assoc 1998; 69: 649-55.
7. Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. CLAO J 1995; 21: 221-32.
8. Jones LT. The lacrimal secretory system and its treatment. Am J Ophthalmol 1966; 62: 47-60.
9. Murube J, Nemeth J, Hoh H, et al. The triple classification of dry eye for practical clinical use. Eur J Ophthalmol 2005; 15: 660-7.
10. Beunckens C, Molenberghs G, Kenward MG. Direct likelihood analysis versus simple forms of imputation for missing data in randomized clinical trials. Clin Trials 2005; 2: 379-86.
11. Friedlaender MH. Ocular manifestations of Sjögren's syndrome: keratoconjunctivitis sicca. Rheum Dis Clin North Am 1992; 18: 591-608.
12. Nelson JD, Farris RL. Sodium hyaluronate and polyvinyl alcohol artificial tear preparations. A comparison in patients with keratoconjunctivitis sicca. Arch Ophthalmol 1988; 106: 484-7.
13. Sullivan LJ, McCurrach F, Lee S, et al. Efficacy and safety of 0.3% carbomer gel compared to placebo in patients with moderate-to-severe dry eye syndrome. Ophthalmology 1997; 104: 1402-8.
14. Marquardt R, Christ T. [Corneal contact time of artificial tear solutions.] Klin Monatsbl Augenheilkd 1986; 189: 254-7.
15. Marner K, Mooller PM, Dillon M, Rask-Pedersen E. Viscous carbomer eye drops in patients with dry eyes. Efficacy and safety. A randomized, open, cross-over, multicentre study. Acta Ophthalmol Scand 1996; 74: 249-52.
16. Brodwall J, Alme G, Gedde-Dahl S, et al. A comparative study of polyacrylic acid (Viscotears) liquid gel versus polyvinylalcohol in the treatment of dry eyes. Acta Ophthalmol Scand 1997; 75: 457-61.
17. Toda I, Shinozaki N, Tsubota K. Hydroxypropyl methylcellulose for the treatment of severe dry eye associated with Sjögren's syndrome. Cornea 1996; 15: 120-8.
18. Diebold Y, Herreras JM, Callejo S, Argueso P, Calonge M. Carbomer- versus cellulose-based artificial-tear formulations: morphologic and toxicologic effects on a corneal cell line. Cornea 1998; 17: 433-40.
19. Marquardt R, Christ T, Bonfils P. [Gelatinous tear substitutes and nonspecific eye ointments in the critical care unit and in perioperative use.] Anaesth Intensivther Notfallmed 1987; 22: 235-8.